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PCT

REC'D 18 OCT 2004
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

26 JAN2005

Applicant's or agent's file reference 4-32595A/HO 59	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/08314	International filing date *(day/month/year)* 28.07.2003	Priority date *(day/month/year)* 29.07.2002
International Patent Classification (IPC) or both national classification and IPC C07J33/00		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.02.2004	15.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Weisbrod, T Telephone No. +49 89 2399-8931

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/08314

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-12 as originally filed

Claims, Numbers

1-7 filed with telefax on 05.10.2004

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 6,7

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 6,7 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 6,7

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I

Basis of the opinion

During the procedure the applicant has filed an amended set of claims. In amended claim 1 reference to crystal form A of compound (I) has been deleted, and original claim 5 (directed to a process for preparing form A of compound I) has been deleted. The amendments comply with the requirements of Article 19(2) and 34(2)(b) PCT.

The application is now directed to

(i) crystal form B of a thiophenecarboxylic acid cyclopenta[a]hydrophenanthrenyl ester (I) (claim 1),
(ii) a pharmaceutical composition comprising these crystal forms (claims 2-3),
(iii) the medical use of these crystal form (claim 4),
(iv) a method for preparing crystal form B of compound (I) (claim 5), and
(v) a crystal form (i.e. at least the forms A and B) "substantially as herein described with reference to the examples resp. drawings" (independent claims 6 and 7).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The ISA has not issued a search report for claims 6 and 7. No International Preliminary Examination has thus been carried out with regard to novelty and inventive step for subject-matter which is not covered by the search report (cf. Rule 66.1(e) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: WO 02/00679 A, 03.01.2002; cited in the application.
D2: Haleblian, J.; McCrone, W. *J. Pharm. Sci.* **1969**, *58*, 911-929.
D3: Caira, M. R. in *Topics Curr. Chemistry* **1998**, *198*, 163-208.

2 Novelty

D1 discloses the present compound (I) (example 26), the corresponding pharmaceutical composition and its medical use (claims 12, 13; and page 12, paragraphs 2 and 3). In this context, the document describes a method for preparing compound (I) comprising its crystallisation from isopropanol as final process step (page 26, last paragraph). Crystallisation conditions other than the solvent (e.g. concentration or temperature profile) are not reported in **D1**.

If the claimed product and the known product are identical except for the parameters through which the claimed product is defined, the onus lies with the applicant to substantiate novelty over the product of the prior art. This would also apply if the claimed product was obtained by a process different from that of the prior art. In the present case, however, the application shows already that equilibrating compound (I) at room temperature in methanol, ethanol, and dichloromethane leads to the claimed crystal form B, whereas equilibrating compound (I) at room temperature in isopropanol affords the crystal form A. The different identity of both forms is shown by the XRPD's of the present figures 1 and 2. In view of the experimental results of the present application and the lack of any further crystallisation conditions in **D1**, it appears justified to conclude that the procedure of **D1** affords compound (I) in the crystal form A, whereas the present claims 1-5 relate to the crystal form B. Hence, the present claims 1-5 appear novel vis-à-vis **D1**.

D2 and **D3** relates to polymorphism of organic compounds. The documents are not relevant to the question of novelty of the application, because compound (I) is not disclosed therein.

3 Inventive Step

3.1 The application describes the preparation and characterisation of the crystal forms A and B of compound (I), which are useful in treating antiinflammatory conditions. Furthermore, the application states that some ("of the two") crystal forms have very good stability, facilitating their use in the preparation of pharmaceutical dosage forms (the application, page 1).

3.2 **D1** discloses compound (I) (crystallised from isopropanol and considered to represent the present crystal form A) as an inhibitor of TNF-alpha synthesis and its use in the manufacture of a medicament for the treatment of an inflammatory condition. **D1** is thus considered to represent the most relevant state of the art.

According to the experimental results presently on file the claimed crystal form B differs from form A of **D1** through certain physicochemical parameters (which is to be expected for polymorphs). In view of **D1** the problem underlying the application is seen in the provision of a further crystal form of compound (I) useful for the preparation of pharmaceutical dosage forms for the same therapeutic application.

Since the pharmaceutical effect of a pharmaceutical active ingredient (in the present case the antiinflammatory activity of the present compound I) is based on its molecular structure rather than on its solid state properties, the present claimed crystal form B of compound (I) is merely an obvious alternative of the crystal form of **D1** for the same therapeutic application. In the absence of any substantiated unexpected effect relevant for the therapeutic application or the processing of the claimed crystal form B in comparison with the crystal form A of **D1**, no inventive step would be acknowledged for the claimed crystal form and subject matter referring to this crystal form. Consequently, the present claims 1-5 do, at present, not involve an inventive step.

In this context the applicant is reminded that according to the common general knowledge of a person skilled in the art most substances when investigated for a sufficiently long time reveal more than one polymorph. Furthermore, in the pharmaceutical industry the systematic investigation of polymorphism is routine practice (cf. **D3**, page 165, last paragraph to page 166, first paragraph). Mere different properties concerning the solubility, bioavailability, density, melting point, or chemical reactivity of the claimed crystal form in comparison with the corresponding properties of the known crystal form would be insufficient to establish an inventive step, because such different properties can be readily expected by the person skilled in the art (cf. e.g. **D2**; or **D3**, page 164, paragraph 1; and page 165, paragraph 2). The diffraction pattern and the melting point with simultaneous decomposition of the claimed crystal form B (with melting and decomposition occurring at 270 °C compared to 264 °C for form A) does not appear relevant for its therapeutic application or processing and, is therefore unsuited to establish an inventive step. Equally, the unpredictability of the diffraction pattern and melting point of a new polymorph is irrelevant for the assessment of inventive step.

3.3 If the applicant, however, would submit that the problem underlying the application was the provision of an improved i.e. thermodynamically more stable crystal form of compound (I), then it is noted that at present no argument has been provided that the claimed crystal form B is in fact thermodynamically more stable than the

crystal form A of **D1**. Under these circumstances, the only basis for accepting that the claimed crystal form would solve the problem posed (i.e. being thermodynamically more stable), would be common general knowledge. The same common general knowledge, however, would be similarly applicable to the assessment whether the solution of the technical problem is to be considered obvious. Hence, in the absence of any substantiation of the technical effect and any instructions how said effect has been assessed, no inventive step would be acknowledged for the claimed matter.

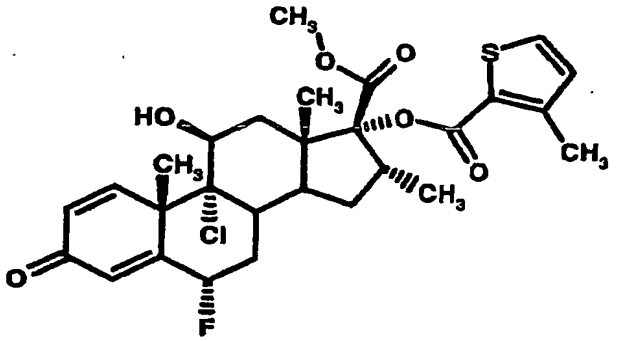
In this context it is furthermore noted that from the higher melting point of the crystal form B alone (without knowing the interrelationship of the crystal forms A and B), it cannot be concluded that the crystal form B would be thermodynamically more stable than the crystal form A, because only in monotropic polymorphic systems the high melting form is at all temperatures thermodynamically more stable than the low melting form. In enantiotropic systems, however, the low melting polymorph is the thermodynamically stable form below the transition temperature, whereas the high melting form is the thermodynamically stable one above the transition temperature. Consequently, it is at present not evident wether the claimed or the known crystal form of compound (I) is the thermodynamically stable one and at which temperature.

4 Deficiencies of the Application under Article 6 PCT

Claims 7 and 8 are to be objected under Article 6 in combination with Rule 6.2(a) PCT for referring to the description. In addition the vague phrase "substantially as herein described" renders the claims incomprehensible.

CLAIMS

1. A compound of formula I



I

in a crystal form B that has a melting point, by Differential Scanning Calorimetry, of about 270°C with simultaneous decomposition, at a heating rate of 20° C/min and the following characteristic diffraction lines (2θ in angular degrees ± 0.2°) in the X-ray diffraction pattern thereof: 7.2°, 9.3°, 12.0°, 12.8°, 13.1°, 14.5°, 17.4°, 20.4°, 23.2° and 25.8°.

2. A pharmaceutical composition comprising, as active ingredient, an effective amount of the compound of formula I in crystal form B as defined in claim 1, optionally together with a pharmaceutically acceptable carrier.

3. A composition according to claim 2, which is in inhalable form.

4. The use of a compound according to claim 1 in crystal form B for the preparation of a medicament for the treatment of an inflammatory or obstructive airways disease.

5. A method of preparing a compound of formula I in crystal form B as defined in claim 1 which comprises crystallising the compound of formula I as defined in claim 1 from a solution thereof in ethanol, methanol or methylene chloride.

6. A crystal form of the compound of formula I, substantially as herein described with reference to any of the Examples.

7. A crystal form of the compound of formula I, substantially as herein described with reference to either of the drawings.